

- (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; citing Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

The claims provided herein now more particularly recite the subject matter of the invention. Namely, Applicants' invention considered as whole is, at a minimum, directed to a method for identifying a nucleic acid sequence. One or more populations of nucleic acid molecules comprising at least one set of nucleic acid sequences are digested with one or more restriction enzymes to produce one or more subpopulations of nucleic acid molecules. The subpopulations are partitioned into fractions having specific fragments from which a library is constructed. Specific fragments are pooled and mapped according to identified parameters. A further partitioning step is performed on the pooled fragments, and the results are analyzed so as to provide one or more selected subsets from which a specific fragment may be selected for sequencing.

On the other hand, Kamb, when considered as a whole, is directed to comparative assessment of the level of specific nucleic acid sequences in samples derived from different sources. Clearly, Kamb addresses a different problem and obtains a different result than that solved by the present invention. The Examiner relies on Kamb for construction of gene libraries. As the Examiner has admitted, Kamb does not teach two fractionation steps as required in claim 27. As applied to new claim 58, Kamb does not teach two partitioning steps, much less suggest identification of nucleic acid sequence as in the present invention. Nowhere in Kamb is there suggestion or motivation to seek a second partitioning step or to identify nucleic acid sequences as claimed. Applicants submit that one of skill in the art would not look to the disclosure in Kamb to identify nucleic acid sequences. The Examiner has effectively failed to consider the teachings of Kamb as a whole and has improperly relied on an arbitrary section in Kamb (*i.e.*, columns 26-27, see Office Action, pages 2-4) to support the rejection.

Further, each and every element of a claimed invention must be disclosed in the art cited for an obviousness rejection. Neither Kamb nor Short describe the pooling of subfractions in a manner that provides for mapping a sequence to its original location in the fractions. Therefore, all elements of the claimed invention are not disclosed in the cited art, making this obviousness rejection is improper.

Nor does the combination of Kamb and Short suggest the desirability to achieve the claimed invention. The disclosure in Short, considered as a whole, addresses a different problem, namely, a process for identifying clones having a specific biological activity of interest. Further, the Examiner relies on Short (Office Action, pages 4-5) for disclosing a normalized library and recovery of "unclonable" sources. The Examiner concludes that it would have been obvious to fractionate both the set and subset because Short is said to describe the separation of nucleic acids from multiple organisms, fractionation of complex mixtures of genomes and amplification of rare or low abundance nucleic acid molecules that can be used in a gene library. However, Short discloses optimization of normalized libraries to screen for bioactivity. Nowhere in Short is there suggestion or desirability to sequence nucleic acid molecules.

The Examiner further asserts:

"...it *would have been* beneficial to fractionate and recover a sample first from a genomic pool, which *would have* allowed for a specific chromosome, chromosome fragment or gene to be separated. Secondly it *would have been* obvious to then create a library from this population and then fractionate this population, recover a subset, and isolate and sequence it. This *would have been* obvious because it *would have* allowed one of ordinary skill in the art to further purify and distinguish specific genes or regions within a gene, which *would have been* impossible to fractionate from an entire genomic population because the entire population *would have been* too large to allow for small sections to be isolated." (Office Action, page 9)

There is no support provided for the Examiner's assertions. The proper test of obviousness is determined by what the combined teachings of prior art references would have suggested to those of ordinary skill in the art (*citations omitted*), not by whether particular combinations of elements from such references might have been "obvious to try". (*In re Fine*, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988)) The Examiner's assertions of **what would have been** amounts to an improper "obvious to try" examination for obviousness. Therefore, the Examiner has not established a *prima facie* case of obviousness.

The Examiner correctly asserts that in the earlier art it "would have been impossible to fractionate from an entire genomic population...." However, Applicants have shown the method of the invention provides the unexpected results that the Examiner asserts would have been impossible. Example 12 of the specification compares the clone complexity with and without use of a sizing step or method of the present invention. See, specification pages 65-66. Figure

4A presents sequencing results that were obtained without the use of the steps comprising the invention as claimed. The top pie chart in FIG. 4B shows the numbers corresponding to the prevalence of a particular clone sequenced. For example, single copies of clones made up 2% of all of the fragments sequenced, while fragments present at greater than 51 copies made up 38% of all of the fragments sequence. The bottom pie chart in FIG. 4B presents sequencing results obtained using the method of the present invention. As the pie chart demonstrates, sizing used in combination with map positions improves the ability to find the low abundance transcripts over fractionation alone. The low abundance transcripts, such as the single to triple copies, now comprise 33% of the total fragments as compared to 8% in the non-sized sequence results. Compare top pie chart with bottom pie chart in FIG. 4B. Applicants submit that none of the references cited by the Examiner accomplishes the unexpected results of the present invention.

According to MPEP 2141, the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. By isolating the disclosure of cols. 26-27 of Kamb, the Office Action appears to have engaged precisely in just such impermissible hindsight.

Furthermore, the deficiencies of Kamb and Short are not overcome by Okayama. Okayama, as a whole, discloses high efficiency cloning of full-length DNA. First, the present invention does not attempt to clone the full-length DNA. Second, Okayama does not suggest digestion of nucleic acid molecules into subpopulations and subsets as in the present invention. Such disclosure would be in direct opposition to the purpose of the disclosure in Okayama. Third, Okayama does not enable mapping of pooled fragments to their original location. Finally, in addition to failing to consider the invention as well as the reference as a whole, the Examiner relies again on an arbitrary paragraph in Okayama (p. 164, right column "DNA sequencing") to support the rejection. Nowhere in Okayama is there suggestion to modify Kamb or Short or to combine their teachings (MPEP Section 2143) to provide the method claimed.

In combining these references, the Examiner has engaged in hindsight reconstruction to pick and choose among unrelated prior art disclosures to deprecate the claimed invention. (*In re Fine* at 1600) According to MPEP 2141, the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. By picking isolated paragraphs from the references representing individual elements of the claims, the Examiner appears to have engaged precisely in just such impermissible hindsight. Therefore the *prima*

*facie* case of obviousness based on Kamb, Short, or Okayama, alone or in combination, cannot prevail.

Finally, Kamb, Short, or Okayama, alone or in combination, do not describe all aspects of the invention. At a minimum, mapping elements presented in the claims depending from claim 58 are not suggested in any way. Indeed, they further render the claimed invention non-obvious in view of the cited references. Applicants also submit that independent claims 72 (sizing to provide multiplex sets, deconvoluting and identifying a nucleic acid sequence) and 73 (sizing to provide multiplex sets, deconvoluting and sequencing) are non-obvious over the cited references.

In view of the foregoing comments, reconsideration and withdrawal is requested of the rejection for obviousness over the combination of Kamb, Short and Okayama.

Claims 43-46 were rejected as obvious over the combination of Kamb, Short, Okayama, and further in view of Macevicz et al., US Patent No. 6,136,537 ("Macevicz"). The rejection is traversed to the extent it is applied to the claims as submitted.

Macevicz, considered as a whole, addresses a different problem from that of identifying a nucleic acid sequence. Specifically, Macevicz relates to a method for analyzing the frequency of sequences in a population of polynucleotides. At a minimum, no mention is made of pooling sequences in a manner that provides for mapping a fragment's original location. Macevicz fails to supply what Applicants have shown to be lacking in Kamb, Short and Okayama. Therefore, Kamb, Short, Okayama or Macevicz, individually or in combination, fail to provide all claimed elements of the invention, thus making this obviousness rejection improper.

Also, according to tenet (B) of MPEP 2141, the Examiner may not consider a portion of a reference, such as col. 2 of Macevicz (see Office Action, pages 10-11), without relating the disclosure to the reference as a whole. Applicants submit that an art worker seeking to identify a nucleic acid sequence would not have turned to a reference, such as Macevicz.

Furthermore, according to MPEP 2141, the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. By isolating the disclosure of col. 2 of Macevicz, the Office Action appears to have engaged precisely in just such impermissible hindsight.

Finally, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference

or to combine reference teachings (MPEP Section 2143). The Examiner cites Macevicz on pages 10- 11 without offering any basis for modifying Kamb, Short and Okayama, or for combining their teachings with those of Macevicz. Therefore, the prima facie case of obviousness based on Kamb in view of Short in view of Okayama, and further in view of Macevicz, also cannot prevail.

In view of the foregoing comments, reconsideration and withdrawal of the rejection is requested.

### CONCLUSION

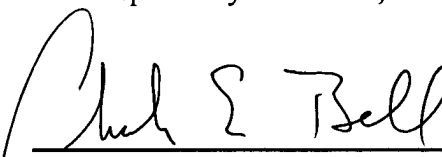
Applicants submit that the application is in condition for allowance and such action is respectfully requested.

Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

A petition for extension of time and fee under 37 C.F.R. 1.17(a)(2) accompany this Amendment and Response. With the extension, this response is due by October 11, 2002. The Commissioner is hereby authorized to charge payment of any additional filing fees required in connection with the papers transmitted herewith, or credit any overpayment of same, to Deposit Account No. 50-0311 (Reference No. 15966-539 CIP).

Respectfully submitted,

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